IN THE CLAIMS

Please cancel claim 36 without prejudice to further prosecution, and amend claims 17 and 37 as follows:

17. (CURRENTLY AMENDED) A method for replacing a target fragment of a gene in a cell, the method comprising delivering to the cell an exogenous replacement DNA fragment, the replacement DNA fragment consisting essentially of:

(a) at least one replacement exon having a 3' end and a 5' end;

(b) a 3' end consisting ~~essentially~~ of a 3' flanking noncoding sequence adjacent to the 3' end of the at least one replacement exon; and

(c) a 5' end consisting ~~essentially~~ of a 5' flanking noncoding sequence adjacent to the 5' end of the at least one replacement exon;

wherein the replacement DNA fragment is from 1 to about 2000 bases and includes less than all of the exons of the gene ~~and does not include vector sequence~~, and wherein the 3' flanking noncoding sequence of the replacement DNA fragment is homologous to and anneals to a 3' flanking noncoding sequence adjacent to the target fragment, and the 5' flanking noncoding sequence of the replacement DNA fragment is homologous to and anneals to a 5' flanking noncoding sequence adjacent to the target fragment, so that the exogenous replacement DNA fragment replaces the target fragment of the gene in the cell.

18. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the cell is *ex vivo*.

19. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the cell is *in vivo*.

20. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the target fragment of the gene in the cell comprises a DNA sequence comprising a genetic defect associated with a disease or dysfunction.

21. (PREVIOUSLY PRESENTED) The method of claim 20, wherein the disease or dysfunction is Fanconi's anemia, cystic fibrosis, sickle cell anemia, thalassaemias, retinitis pigmentosa, xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, retinoblastoma, Duchenne's muscular dystrophy, Lesch Nyhan syndrome, adenosine deaminase deficiency or Tay-Sachs disease.

22. (PREVIOUSLY PRESENTED) The method of claim 20, wherein the target fragment of the gene is a DNA sequence present in the cystic fibrosis gene.

23. (PREVIOUSLY PRESENTED) The method of claim 20, wherein the target fragment of the gene is a DNA sequence present in the sickle cell anemia gene and the target fragment is replaced with a replacement genomic DNA sequence encoding a region of β-globin.

24. (PREVIOUSLY PRESENTED) The method of claim 20, wherein the target fragment of the gene is a DNA sequence present in the gene causing thalassaemias, wherein the sequence is replaced with a replacement genomic DNA sequence in the thalassaemias causing genomic loci.

25. (PREVIOUSLY PRESENTED) The method of claim 20, wherein the target fragment of the gene is a DNA sequence present in a gene causing xeroderma pigmentosum.

26. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the replacement DNA fragment is single stranded.

27. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the replacement DNA fragment is double stranded.

28. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the delivering of the exogenous replacement DNA fragment comprises delivery by electroporation, microinjection, complexing the exogenous replacement DNA fragment in a lipid layer, complexing the exogenous

replacement DNA fragment in a cationic lipid, complexing the exogenous replacement DNA fragment in a dendrimer or conjugating the exogenous replacement DNA fragment to polylysine.

29. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the method is carried out in a population of cells containing the target fragment of the gene, and further comprising determining the extent of homologous replacement by identification of cells within the population that have replaced the target fragment of the gene with the exogenous replacement DNA fragment at a target genomic locus, wherein the identification comprises PCR or Southern hybridization.

30. (PREVIOUSLY PRESENTED) The method of claim 29, wherein the exogenous replacement DNA fragment is identified using primers of about 25 bases that are outside of regions of homology defined by the exogenous replacement DNA fragment, or primers that are allele-specific and differentiate between the target fragment of the gene and the exogenous replacement DNA fragment, or by Southern hybridization with allele-specific oligonucleotide probes that differentiate between the target fragment of a gene and the exogenous replacement DNA fragment.

31. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the exogenous replacement DNA fragment is uncoated or coated with a recombinase or complexed with a protein, provided that the recombinase is not recA.

32. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the exogenous replacement DNA fragment is generated by PCR amplification, oligonucleotide synthesis, plasmid cleavage with restriction endonuclease or by a combination of restriction enzyme cleavage of plasmid inserts and ligation of contiguous insert fragments.

33. (PREVIOUSLY PRESENTED) The method of claim 32, wherein the PCR amplification is performed with primers specific for the exogenous replacement DNA fragment.

34. (PREVIOUSLY PRESENTED) The method of claim 33, wherein the target fragment of a gene is a DNA sequence present in the cystic fibrosis gene, and the primers are selected from the

group consisting of primers CF1, CF1B, CF5, CF6, CF7B, CF8B, CF7C, CF8C, CF9, CF14, CF17 and CF22.

35. (PREVIOUSLY PRESENTED) The method of claim 33, wherein the target fragment of a gene is a DNA sequence present in the sickle cell anemia gene, the target fragment is replaced with a replacement genomic DNA sequence encoding a region of β-globin, and the primers are selected from the group consisting of primers SC1(+), SC2(-), SC3(+), SC4(-), SC5(+), SC6(-), SC-BA(-) and SC- BS(-).

36. (CANCELLED)

37. (CURRENTLY AMENDED) A composition comprising a replacement DNA fragment and a delivery vehicle suitable for delivery of the replacement DNA fragment into a cell containing a target fragment of a gene, wherein the replacement DNA fragment consists essentially of:

(a) at least one replacement exon having a 3' end and a 5' end;

(b) a 3' end consisting ~~essentially~~ of a 3' flanking noncoding sequence adjacent to the 3' end of the at least one replacement exon; and

(c) a 5' end consisting ~~essentially~~ of a 5' flanking noncoding sequence adjacent to the 5' end of the at least one replacement exon;

wherein the replacement DNA fragment includes less than all of the exons of the gene ~~and does not include vector sequence~~, wherein the delivery vehicle comprises a lipid, a dendrimer or polylysine, and wherein the 3' flanking noncoding sequence of the replacement DNA fragment is homologous to and anneals to a 3' flanking noncoding sequence adjacent to the target fragment, and the 5' flanking noncoding sequence of the replacement DNA fragment is homologous to and anneals to a 5' flanking noncoding sequence adjacent to the target fragment, so that the exogenous replacement DNA fragment replaces the target fragment of the gene upon delivery of the replacement DNA fragment into the cell.

38. (PREVIOUSLY PRESENTED) A method for gene therapy comprising contacting a cell with the composition of claim 37 so that the replacement DNA fragment is delivered into the cell and corrects a genetic defect in the target fragment of the gene in the cell.

39. (PREVIOUSLY PRESENTED) The method of claim 38, wherein the contacting occurs *ex vivo*.

40. (PREVIOUSLY PRESENTED) The method of claim 38, wherein the contacting occurs *in vivo*.

41. (PREVIOUSLY PRESENTED) The method of claim 17, wherein the cell is a mammalian cell.

42. (PREVIOUSLY PRESENTED) The method of claim 41, wherein the mammalian cell is a human cell or a mouse cell.

43. (PREVIOUSLY PRESENTED) The method of claim 38, wherein the cell is a mammalian cell.

44. (PREVIOUSLY PRESENTED) The method of claim 43, wherein the mammalian cell is a human cell.

REMARKS

I. INTRODUCTION

In response to the Office Action dated March 26, 2003, claims 17 and 37 have been amended, and claim 36 has been cancelled. Claims 17-35 and 37-44 remain in the application. Entry of these amendments, and reconsideration of the application, as amended, is requested.

II. CLAIM AMENDMENTS

Applicants' attorney has made amendments to the claims as indicated above. These amendments are supported by the application as originally filed and do not introduce new matter. Claim 17 has been amended to include all the limitations of cancelled claim 36. The amendment to claim 37 is supported by the specification, e.g., at page 70, lines 32-35. Entry of these amendments is respectfully requested.

Each of claims 17 and 37 has been amended to delete "essentially" from parts (b) and (c). This amendment serves to clarify that the flanking sequence at both the 3' and 5' ends of the exogenous replacement fragment must be noncoding sequence that is homologous to and anneals to the 3' and 5' noncoding sequence that flanks the target fragment of the gene in the cell. It is understood that, to the extent minor modifications to the flanking sequence could be made without departing from the spirit and scope of the invention, such modified flanking sequence would still retain the property of being homologous to and annealing to flanking sequence of the target fragment. Accordingly, this amendment clarifies without narrowing the scope of the independent claims by obviating argument as to whether "consisting essentially of" means additional sequence could be included beyond the 3' and 5' flanking sequence as recited in the claims.

III. INTERVIEW SUMMARY

Reference is made to a telephonic interview conducted on September 10, 2003, between Examiner Katcheves and Applicants' undersigned attorney. The interview related to the nature and purpose of the claim amendments requested but not entered from the Amendment submitted on July 28, 2003. In particular, the discussion centered on the transitional phrase "consisting essentially of" and the appropriate interpretation of this phrase in the context of the subject application. The

discussion that follows in Section IV of these Remarks addresses any potential concerns regarding the clarity and meaning of this transitional phrase as used in Applicants' claims.

IV. MEANING OF "CONSISTING ESSENTIALLY OF" IN CLAIMS

Independent claims 17 and 37 have retained the phrase "consisting essentially of" in the preamble in connection with the phrase "replacement DNA fragment". MPEP §2111.03 states that the "transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention" (citing *in re Herz*, 537 F.2nd 549, 551-552, 190 USPQ 461, 463 (CCPA 1976), *emphasis in original*). It is improper to disregard the distinction between the transitional phrases "comprising" and "consisting essentially of".

Applicants state for the record that the basic and novel characteristics of the claimed invention involves use of small fragments for targeted replacement of a gene in a cell which relies on use of flanking noncoding sequence in the exogenous replacement fragment that is homologous to and anneals to flanking noncoding sequence of the target fragment in the gene of the cell. This statement is supported by the specification, for example, at page 22, lines 3-11. Accordingly, the transitional phrase "consisting essentially of", as used in claims 17 and 37, indicates that additional material beyond the flanking noncoding sequence of the replacement fragment would materially affect the basic and novel characteristics of the claimed invention. It would therefore be improper to construe "consisting essentially of" as meaning "comprising" or as encompassing a replacement fragment that includes an entire genomic sequence, for example, or is flanked by an additional exon that is not flanked by noncoding sequence.

V. NON-ART REJECTIONS

A. Double Patenting Rejection

At page 2 of the Office Action, claims 17, 20-26 and 28-36 were rejected under the judicially created doctrine of obviousness-type double-patenting in view of claims 1-10 and 12 of prior U.S. Patent No. 6,010,908. Applicants will provide a terminal disclaimer upon identification of allowable subject matter.

B. Enablement Rejection

At page 3 of the Office Action, claims 18, 19, 38-40 and 43-44 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 3 of the Office Action, claims 17, 20-36 and 41-42 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for replacing a target fragment in a cell *in vitro*, is regarded as not reasonably providing enablement for a method of replacing a target fragment *in vivo* or *ex vivo*, wherein the cells are intended for gene therapy use, and it is alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants respectfully traverse these rejections.

Applicants incorporate the arguments raised in the Amendment dated December 3, 2001, but will refrain from re-stating these arguments here to keep the discussion focussed on the remaining issues that are most relevant to clarifying why the pending claims are in fact enabled by the specification as originally filed.

1. Successful Replacement of Target Fragment Occurs *In Vivo* and *Ex Vivo*

As acknowledged at page 3 of the Office Action, there is no dispute that the specification is enabling for replacing a target fragment of a gene in a cell *in vitro*. The remaining issue is whether the teachings of the specification enable a method of replacing a target fragment *in vivo* or *ex vivo*, wherein the cells are intended for gene therapy use. Although the arguments and evidence presented herein demonstrate that the specification is enabling for gene therapy use, it is respectfully noted that gene therapy is not the only use for *in vivo* and *ex vivo* target replacement contemplated by the application. The Examiner's attention is directed to pages 58-63 of the specification, which discuss application of the methods of the invention to the production of transgenic animals and an animal model for disease, such as cystic fibrosis.

In addition to the evidence and arguments submitted with the Amendment dated December 3, 2001, Applicants submit herewith further evidence that the method for replacing a target

fragment of a gene in a cell practiced in accordance with the teachings of the specification is successful. More specifically, recent work has confirmed that the claimed method (small fragment homologous replacement, or SFHR) results in:

(1) replacement of the target fragment with the replacement fragment in both *in vivo* and *ex vivo* model systems;

(2) complete replacement at both alleles;

(3) subsequent expression of the replacement fragment in human hematopoietic stem/progenitor cells (HSPC) following SFHR-mediated modification of β-globin sequences;

(4) stable inheritance of the replacement fragment at the chromosomal level;

(5) successful engraftment of SFHR-modified cells in immune deficient mice, showing both efficient and stable conversion of β-globin in HSPC; and

(6) functional correction of ion transport properties to normal ranges in the nasal mucosa in SFHR-treated mice in an *in vivo* model of cystic fibrosis.

The data supporting the above are described in a Declaration Under 37 C.F.R. §1.132 by inventor Dr. Dieter Gruenert submitted herewith. SFHR-mediated modification of β-globin sequences in the *ex vivo* system is described in two manuscripts recently submitted for publication and appended to the Declaration as Exhibits A (Prokopishyn et al.) and B (Goncz et al.). The SFHR-mediated modification of ion transport in nasal mucosa in a mouse model of cystic fibrosis is described in paragraph 6 of Dr. Gruenert's Declaration submitted herewith.

These data establish that the claimed method can correct a defective gene with sufficient efficiency to achieve a therapeutic effect, and that it works both *in vivo* and *ex vivo*. Successful replacement has been achieved using both lipid-based (lipofectamine, lipofectin®) and mechanical delivery systems (microinjection, electroporation). Both of these strategies are described in the specification (e.g., microinjection at page 23, lines 25-30; and lipid-based delivery at page 42, line 11, at page 73, line 12, and at page 75, line 32, to page 76, line 14). In addition, the variety of suitable delivery approaches is discussed in the specification at page 24, lines 25-29, and at page 40, as well as throughout the Examples portion. Accordingly, the person skilled in the art as of the filing date of this application could have practiced the claimed invention by following the teachings of the specification.

2. Guidance and Teachings of Specification Are Sufficiently Enabling

At page 6 of the Office Action, it is alleged that:

> The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, particularly low efficiency of delivery of the nucleic acid. There is no direction on how to ensure that cells from the ex vivo method would replace, or otherwise out-compete, the endogenous defective cells.

In response, Applicants respectfully note that the vast majority of the 102-page specification of the present application provides extensive guidance to support the claimed invention for gene therapy applications (see, e.g., pages 21-25; 54-56; 69-77; and Examples). The stated object of the invention is explicitly directed at overcoming the recognized obstacles of low efficiency of delivery of nucleic acids (see, e.g., page 13, lines 8-9; page 22, lines 3-11; page 77, lines 13-31). The very purpose of the patent system, "to promote progress in the useful arts", is served by inventions such as this one, designed to address a recognized problem. It was the fact that the problem had not already been solved that served as the basis for the present invention.

The Examiner cites the evidence of the problem (the fact that prior art methods of gene therapy via delivery of an entire gene have not worked well) as a basis for questioning a novel solution (the use of small fragments with flanking noncoding sequences). The Examiner is respectfully reminded that the basis for questioning enablement of the claimed method must be directed at the claimed method itself, and not at the shortcomings of the prior art. No basis has been provided for doubting the reasoning and evidence provided in support of Applicants' claimed method.

3. Previously Submitted Evidence Should Not Be Dismissed

At page 9 of the Office Action, each of the five articles submitted with the Amendment dated December 3, 2001, was dismissed as not showing enablement for the *in vivo* methods. Three of the articles were dismissed without discussion because they were *in vitro* studies. These studies were still relevant, however, because they show that functional correction accompanies successful replacement of a target fragment. For example, the Kunzelmann et al. article (1996, Gene Therapy 3:859-867; Exhibit D of 12/3/01) showed that correction of the ΔF508 fragment with wild type sequence does in fact restore chloride transport, thereby correcting the functional defect that

characterizes cystic fibrosis. Exhibit E of 12/3/01, Goncz et al. (1998, Human Molecular Genetics 7(12):1913-1919) showed that this correction occurs in non-transformed primary human airway epithelial cells, the very target cells of an *in vivo* gene therapy for cystic fibrosis. These *in vitro* studies augment the *in vivo* and *ex vivo* studies because they confirm that the method of replacement works in normal target cells as well as in transformed cells, and that reasonable inferences about functional correction can be drawn from structural evidence of target replacement.

Interestingly, the Examiner also dismissed without discussion Exhibit G of 12/3/01, which explicitly supports *ex vivo* SFHR, showing that a replacement fragment remained stable in human hematopoietic stem/progenitor cells for 5 weeks and occurred in up to 70% of the alleles in the outgrowth population of cells. Exhibit G also demonstrated that this SFHR method worked with both microinjection and DNA-lipid complex delivery, both methods taught in Applicants' specification. These data from the *ex vivo* model system address the Examiner's concern that cells modified by the method of the invention are able to successfully repopulate and compete with endogenous unaltered cells.

The *in vivo* studies, Exhibits C and F, were also dismissed by the Examiner because they did not use the same delivery vehicle as Applicants' Example 15. As noted above, however, Applicants' specification teaches a wide range of delivery systems for SFHR, including lipid-DNA complexes, lipofectin® and lipofectamine (see, e.g., page 24, lines 25-29; page 40; page 42, line 11; page 73, line 12; page 75, line 32, to page 76, line 14). Accordingly, these data were developed using methods taught by Applicants' specification.

Applicants respectfully urge the Examiner reconsider the evidence submitted with the Amendment dated December 3, 2001, in addition to the more recent evidence submitted herewith, and withdraw the rejections under 35 U.S.C. §112, first paragraph.

VI. PRIOR ART REJECTIONS

At page 3 of the Office Action, claims 17-20, 27-30, 32, and 37-44 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Berns (U.S. Patent No. 5,789,215). At page 3 of the Office Action, claims 17-20, 26-29, 31, and 37-44 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Vega (Human Genetics (1991) 87:245-253). At page 3 of the Office Action, claims 17, 20, 21, 23, 27-30, 32, 37, 41 and 42 were rejected under 35 U.S.C. §102(b) as allegedly anticipated

by Shesely (Proc. Nat'l Acad. Sci. USA (1991) 88:4294-4298). At page 3 of the Office Action, claims 17, 18, 20-22, 27-32, 37-39 and 41-44 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Kay (U.S. Patent No. 5,612,205). At page 3 of the Office Action, claim 37 was rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tsui (WO 91/10734). At page 4 of the Office Action, claims 17-20, 26-29, 31, and 36-44 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Vega (Human Genetics (1991) 87:245-253). Applicants respectfully traverse these rejections.

A. "Consisting Essentially of" Is Not Open Claim Language

The rejections based on the prior art are based on teachings that relate to large (4.7 kb) targeting constructs that include an entire gene as well as surrounding sequence and an additional oligomer (Shesely) or large fragments that must first be combined to form a correcting sequence of 50 kb or more (Kay) or replacement of entire genes (Vega) that "may comprise at least one exon and 5' and 3' flanking intronic sequences" (Office Action, page 11, first paragraph). The language of these rejections implies that the Examiner continues to interpret "consisting essentially of" in Applicants' claims to mean the equivalent of "comprising". This construction of the claim language renders "consisting essentially of" meaningless. Applicants respectfully urge the Examiner reconsider this construction of the transitional phrase, particularly in view of the statement provided in section III above.

As Applicants believe the Examiner realizes, the intention is to cover the inventive method which involves use of small fragments for targeted replacement of a gene in a cell which relies on use of flanking noncoding sequence in the exogenous replacement fragment that is homologous to and anneals to flanking noncoding sequence of the target fragment in the gene of the cell. To eliminate this issue from discussion and facilitate prosecution, Applicants have amended claims 17 and 37 to delete "essentially" from the recitation relating to the flanking sequences of the exogenous replacement fragment. In addition, Applicants have incorporated the limitations of claim 36 into claim 17 to define the intended meaning of "small" in small fragment homologous replacement. Applicants believe these amendments to the claims should obviate the rejections based on the prior art. To clarify that the claimed invention is free of each of the cited references, Applicants address each in turn below.

B. The Prior Art Fails to Teach or Suggest All Features of Claimed Invention

Applicants respectfully request the Examiner consider all the limitations of the claims when evaluating the prior art rejections. Independent claim 17 recites a method for "replacing a target fragment of a gene" in a cell, not a method for replacing entire genes. Claim 17 also requires the replacement fragment include "less than all of the exons of the gene" to further clarify this limitation. In addition, the claim requires flanking noncoding sequence at both the 3' and 5' ends of the replacement fragment, which flanking sequence is homologous to and anneals to noncoding sequence adjacent to the target fragment. Because claim 17 further requires the replacement fragment be from 1 to about 2000 bases, it does not encompass prior art methods which presumed that entire genes or large portions of sequence were necessary to achieve homologous recombination. Applicants maintain that none of the cited references, alone or in combination, teach or suggest the claimed invention because the prior art did not appreciate Applicants' novel discovery that, in order to successfully target replacement to a specified portion of a gene, such small, discreetly targeted fragments must include flanking noncoding sequence.

Berns teaches use of substantially isogenic replacement DNA molecules using large targeting constructs, such as the 10.5 kb targeting fragment described in Example 1. Although Berns emphasizes the importance of using a replacement fragment that is substantially isogenic with the target DNA, Berns fails to appreciate the importance of flanking noncoding sequence nor does Berns contemplate the potential for use of small fragments.

Vega is a review article that discusses three general strategies for homologous recombination for use in gene therapy: (1) insertional mutagenesis; (2) gene addition; and (3) gene correction. The first two involve insertion and do not pertain to replacement. Discussion of the third strategy, correction, considers use of replacement vectors that produce only the changes necessary for correction and acknowledges the problem with attempting to address this strategy with cDNA fragments because they may lack potentially important introns (see page 246). Even this speculative contemplation of potential future use of small replacement fragments fails to suggest the value of flanking noncoding sequence at both the 3' and 5' ends adjacent to the at least one exon of the replacement fragment.

Shesely teaches use of a 4.7 kb targeting construct that includes the β^A-globin gene plus surrounding sequence and a 20 base pair oligomer in addition to the neomycin resistance gene. Shesely

does not teach or suggest use of a replacement fragment having less than all exons of a gene and flanking noncoding sequence at both the 3' and 5' ends adjacent to the at least one exon of the replacement fragment.

Kay teaches use of large fragments that must first be combined to form a correcting sequence of 50 kb or more. Kay does not teach or suggest use of a replacement fragment having less than all exons of a gene and flanking noncoding sequence at both the 3' and 5' ends adjacent to the at least one exon of the replacement fragment.

The rejection of claim 37 as anticipated by Tsui is rendered moot by the amendment to claim 37 to recite the delivery vehicle. The combination of a PCR fragment of Tsui with a delivery vehicle that comprises a lipid, a dendrimer or polylysine is not taught or suggested by the prior art.

Accordingly, Applicants respectfully request the Examiner reconsider and withdraw each of the rejections based on the prior art.

VII. CONCLUSION

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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